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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,410	12/28/2000	Gloria C. Li	55672-A-PCT-US/ JPW/AJM/M	6916
57539 7	7590 06/26/2006		EXAMINER	
COOPER & DUNHAM LLP			ZARA, JANE J	
1185 AVENUE OF THE AMERICAS NEW YORK, NY 10036			ART UNIT	PAPER NUMBER
142W Torcie,	1 10050		1635	
			DATE MAILED: 06/26/2006	

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary		Application No	. Applicant(s)	Applicant(s)			
		09/750,410	LI ET AL.				
		Examiner	Art Unit				
		Jane Zara	1635				
Period fo	The MAILING DATE of this communic or Reply	ation appears on the cove	er sheet with the correspondence	e address			
WHIC - Exte after - If NC - Failu Any	ORTENED STATUTORY PERIOD FOCHEVER IS LONGER, FROM THE MAINSIONS of time may be available under the provisions of SIX (6) MONTHS from the mailing date of this community period for reply is specified above, the maximum statute to reply within the set or extended period for reply with reply received by the Office later than three months after the patent term adjustment. See 37 CFR 1.704(b).	ILING DATE OF THIS C 37 CFR 1.136(a). In no event, how nication. Itory period will apply and will expire ill, by statute, cause the application	OMMUNICATION. vever, may a reply be timely filed a SIX (6) MONTHS from the mailing date of to become ABANDONED (35 U.S.C. § 133	this communication.			
Status							
1) 又	Responsive to communication(s) filed	on 08 May 2006.					
2a)⊠	This action is FINAL . 2b		nal.				
3)	3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is						
	closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.						
Disposit	ion of Claims						
4)⊠	∑ Claim(s) <u>1,15,16 and 18-22</u> is/are pending in the application.						
•	4a) Of the above claim(s) is/are withdrawn from consideration.						
5)	Claim(s) is/are allowed.						
6)⊠	Claim(s) <u>1,15,16,18-22</u> is/are rejected.						
7)	Claim(s) is/are objected to.						
8)□	Claim(s) are subject to restricti	on and/or election require	ement.				
Applicat	ion Papers						
9)[The specification is objected to by the	Examiner.					
10)	The drawing(s) filed on is/are:	a)⊡ accepted or b)⊡ ot	jected to by the Examiner.				
	Applicant may not request that any object	ion to the drawing(s) be hele	d in abeyance. See 37 CFR 1.85(a).			
	Replacement drawing sheet(s) including to	he correction is required if the	ne drawing(s) is objected to. See 3	37 CFR 1.121(d).			
11)	The oath or declaration is objected to I	by the Examiner. Note th	e attached Office Action or form	n PTO-152.			
Priority (under 35 U.S.C. § 119						
• —	Acknowledgment is made of a claim fo ☐ All b)☐ Some * c)☐ None of:						
	1. Certified copies of the priority documents have been received.						
	2. Certified copies of the priority d						
	3. Copies of the certified copies of	<u></u>		onai Stage			
* (application from the Internation See the attached detailed Office action	•					
	bee the attached detailed Office action	ior a list of the certified c	opies not received.				
Attachmen	t(s)						
1) Notic	e of References Cited (PTO-892)	4)	Interview Summary (PTO-413)				
	e of Draftsperson's Patent Drawing Review (PT	The state of the s	Paper No(s)/Mail Date Notice of Informal Patent Application	ı (PT∩-152)			
	mation Disclosure Statement(s) (PTO-1449 or Par No(s)/Mail Date	(9) (10/2R/08)	Other:	(1 1 0- 102)			

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This Office action is in response to the communication filed 5-8-06.

Claims 1, 15, 16, 18-22 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 15, 16 and 18-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 39 and 40 of copending Application No. 10/712,642 for the reasons of record set forth in the Office action mailed 8-15-05.

No arguments have been provided addressing this rejection.

New Rejections

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Takiguchi et al for the reasons of record set forth in the Office action mailed 2-3-06.

Applicant's arguments filed 5-8-06 have been fully considered but they are not persuasive. Applicants argue that the Takiguchi does not anticipate or render obvious the instant invention because this reference does not meet all of the structural limitations of the instantly claimed invention, which include a functional characterization of the ability to bind and prevent expression of human DNA-dependent protein kinase subunit, Ku70. Applicant also argues that an oligonucleotide that prevents expression of the nucleic acid cannot also be used as a primer (e.g., for detection or amplification of the strand to which it specifically binds).

Contrary to Applicant's assertions, several antisense oligonucleotides are disclosed by Takiguchi that specifically hybridize to various regions of the nucleic acid encoding human and mouse DNA-dependent protein kinase subunit, Ku70 (see Takiguchi at p. 130, both columns, where reverse and forward primers derived from the human and mouse Ku70 were used for the cloning and characterization of a mouse

Ku70 clone). The fact that oligoucleotides are used as probes or primers does not negate their ability to bind a target nucleic acid and, under the proper conditions, inhibit its expression. As mentioned in the prior Office action, where the antisense oligonucleotides of the prior art (e.g., as disclosed by Takiguchi) and the claimed antisense oligonucleotides are identical or substantially identical, or are produced by identical or substantially identical processes such as designing oligonucleotides to target a nucleic acid construct based on its nucleotide sequence, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products.

See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." Therefore, absent evidence to the contrary, since the oligonucleotides disclosed by Takiguchi et al meet all of the structural limitations of the instantly claimed invention, they would necessarily be <u>presumed</u> to have the functionality claimed, of specifically binding to and inhibiting the expression of human Ku70 in vitro. For these reasons, the prior art rejection is maintained.

Rejections Necessitated by Amendment Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 15, 16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takiguchi et al as applied to claim 15 above, Reeves et al and Milner et al, the combination in view of Au-Young et al.

The claims are drawn to compositions and methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an antisense oligonucleotide and optionally further comprising a ribozyme, specifically targeting a nucleic acid encoding a human DNA dependent protein kinase subunit (Ku70), which antisense inhibits the expression of the target human Ku70 subunit, and which antisense is in an appropriate expression vector, operably linked to a heat shock promoter.

Takiguchi (Genomics <u>35</u>: 129-135, 1996) is relied upon as set forth in the 102/103 rejection. Takiguchi et al teach the role of mouse and human DNA-PK (comprising the subunits Ku70, Ku80 and DNA-PK catalytic subunit) in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function. Takiguchi teaches the DNA-dependent protein kinase (DNA-PK) comprising Ku70,

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Ku80 and the DNA-PK catalytic subunit, which DNA-PK functions in DNA double-strand break repair (see 1st & 3rd full paragraph on p. 129). Takiguchi also teaches that the Ku70/80 heterodimer portion of the DNA-PK binds with high affinity to the end of double stranded DNA, and to a single stranded DNA transition (see 2nd full paragraph on p. 129), and recruits and activates the DNA catalytic subunit of the DNA-PK (see 3rd full paragraph on p. 129). Takiguchi teaches the role of Ku70 in DNA double strand repair (see bridging paragraph, pp. 133-134). Takiguchi teaches the motivation to establish experimental mouse models for studying the role of DNA-PK in human diseases (see last paragraph of the article, bridging pp. 133-134).

Reeves et al (J. Biol. Chem., Vol. 264(9): 5047-5052, 1989) teach the polynucleotide sequence encoding human DNA-PK subunit Ku70, and Ku70's binding to the ends of double stranded DNA in a complex with Ku80 (see especially figure 4 on p. 5050 and the text on p. 5047).

Milner et al (Nature Biotech. <u>15</u>: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

The primary references of Takiguchi et al, Reeves et al and Milner et al do not teach methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an antisense oligonucleotide specifically targeting a nucleic acid encoding Ku70, and which antisense is in an appropriate expression vector, operably linked to a heat shock promoter, and optionally linked to a ribozyme.

Au-Young et al (USPN 5,773,580) teach pharmaceutical compositions comprising antisense oligonucleotides for inhibiting a known target gene, as well as teaching expression vectors comprising antisense oligonucleotides and ribozymes, which oligonucleotides are operably linked to regulatory elements including an inducible (heat shock) promoter (see esp. col. 10-11, 20-21). Au-Young teaches the transfection of target cells comprising the administration of compositions comprising nucleic acids and liposomes (col. 24, lines 1-6).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of Ku70 in vitro because its nucleotide sequence had been taught previously by Reeves et al, and Milner et al teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro using routine screening assays that are well known in the art (see Milner at pages 539-540). Milner et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides human DNA dependent protein kinase subunits, including Ku70.

It would have been obvious to one of ordinary skill in the art to insert antisense oligonucleotides into an appropriate expression vector, operably linked to an inducible promoter including a heat shock promoter, because such expression systems have been used routinely in the art for expression of nucleic acid constructs including antisense and ribozymes in an appropriate target cell, as taught previously by Au-Young et al. One of ordinary skill in the art would have been motivated to operably link an antisense oligonucleotide to an inducible promoter in an appropriate expression vector in order to control the conditions of expression of the operably linked antisense, and in order to control conditions for antisense expression and subsequent inhibition of the antisense's target gene in an appropriate target cell. It would have been obvious to one of ordinary skill in the art to administer compositions comprising nucleic acids and liposomes to target cells because this was a routine method in the art, as taught by many including Au-Young. One of ordinary skill in the art would have been motivated to administer compositions of nucleic acids and liposomes because it was well known in the art at the time the invention was made that liposomes enhance the cellular uptake of nucleic acid compositions. One of ordinary skill in the art would have expected that compositions comprising liposomes and nucleic acids would have increased cellular uptake than compositions without liposomes because it is well known in the art that liposomal formulations enhance target cell membrane solubility and the eventual cellular uptake of otherwise polar compounds such as nucleic acids.

One of ordinary skill in the art would have been motivated to target and inhibit the expression of the various subunits of DNA-PK, including Ku70, in order to increase a

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target cell's sensitivity to DNA damaging agents because Takiguchi et al teach the relationship between increasing cell radiosensitivity or loss of DNA repair function, and loss of functional DNA-PK. One of ordinary skill in the art would have been motivated to inhibit the expression of Ku70 in order to increase a target cell's sensitivity to DNA repair because it was well known in the art at the time of the invention that Ku 70 is involved in double stranded DNA repair and it was also well known that strand repair occurs in cells following DNA damage (e.g. strand breaks). One of ordinary skill in the art would have expected that a cancer cell would undergo DNA repair after its exposure to DNA damaging agents. And one of ordinary skill in the art would be motivated to undermine a cancer cell's ability to repair DNA after treating it with DNA damaging agents in order to eventually undermine that cancer's ability to survive.

One of ordinary skill in the art would have expected that by utilizing appropriate conditions for expression (e.g. induction by heat), the antisense targeting DNA-PK would be expressed upon induction of the heat shock promoter because such induction systems as heat shock promoters have been routinely used as described by Au-Young et al. One of ordinary skill in the art would have been motivated to induce expression of antisense and ribozymes under desired conditions (e.g. upon exposure heat) because induction is a way of controlling the conditions for increased expression of the operably linked antisense and ribozymes, and also a way of controlling the subsequent inhibition of target gene expression following expression of these antisense. In this way, increasing a cell's sensitivity to DNA damaging agents is in turn induced following heat treatment and expression of antisense. Therefore the invention as a whole would have

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been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 11-18-05 and 2-3-06 have been fully considered but they are not persuasive. Applicant argues that the combined teachings of Takiguchi, Reeves, Milner and Au-Young fail to properly support a prima facie case of obviousness for several reasons.

Applicant's arguments filed 5-8-06 have been fully considered but they are not persuasive. Applicants argue that the Takiguchi does not anticipate or render obvious the instant invention because this reference does not meet all of the structural limitations of the instantly claimed invention, which include a functional characterization of the ability to bind and prevent expression of human DNA-dependent protein kinase subunit, Ku70. Applicant also argues that an oligonucleotide that prevents expression of the nucleic acid cannot also be used as a primer (e.g., for detection or amplification of the strand to which it specifically binds).

Contrary to Applicant's assertions, several antisense oligonucleotides are disclosed by Takiguchi that specifically hybridize to various regions of the nucleic acid encoding human and mouse DNA-dependent protein kinase subunit, Ku70 (see Takiguchi at p. 130, both columns, where reverse and forward primers derived from the human and mouse Ku70 were used for the cloning and characterization of a mouse Ku70 clone). The fact that oligoucleotides are used as probes or primers does not negate their ability to bind a target nucleic acid and, under the proper conditions, inhibit its expression. As mentioned in the prior Office action, where the antisense

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oligonucleotides of the prior art (e.g., as disclosed by Takiguchi) and the claimed antisense oligonucleotides are identical or substantially identical, or are produced by identical or substantially identical processes such as designing oligonucleotides to target a nucleic acid construct based on its nucleotide sequence, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products.

See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." Therefore, absent evidence to the contrary, since the oligonucleotides disclosed by Takiguchi et al meet all of the structural limitations of the instantly claimed invention, they would necessarily be <u>presumed</u> to have the functionality claimed, of specifically binding to and inhibiting the expression of human Ku70 in vitro. For these reasons, the prior art rejection is maintained.

Applicant argues that they have made the surprising discovery of Ku70's role in DNA double stranded breaks repair and therefore the invention was not obvious. Contrary to Applicant's assertions, Takiguchi in 1996 repeatedly taught Ku70's role in DNA double stranded breaks repair. Takiguchi teaches the DNA-dependent protein kinase (DNA-PK) comprising Ku70, Ku80 and the DNA-PK catalytic subunit, which DNA-PK functions in DNA double-strand break repair (see 1st & 3rd full paragraph on p.

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129). Takiguchi also teaches that the Ku70/80 heterodimer portion of the DNA-PK binds with high affinity to the end of double stranded DNA, and to a single stranded DNA transition (see 2nd full paragraph on p. 129), recruits and activates the DNA catalytic subunit of the DNA-PK (see 3rd full paragraph on p. 129). Takiguchi teaches the role of Ku70 in DNA double strand repair (see bridging paragraph, pp. 133-134). So, contrary to Applicant's assertions, the role of Ku70 in DNA double strand breaks repair was not a surprising finding at the time the instant application was filed.

Applicant argues that Takiguchi teaches mouse and not human Ku70 and that since the relationship between mouse and human Ku70 has not been established, Takiguchi cannot render the instant invention obvious. Contrary to Applicant's assertions, Takiguchi teach the role of mouse and human DNA-PK in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function. Takiguchi teaches the DNA-dependent protein kinase (DNA-PK) comprising Ku70, Ku80 and the DNA-PK catalytic subunit, which DNA-PK functions in DNA double-strand break repair (see 1st & 3rd full paragraph on p. 129). Takiguchi also teaches that the Ku70/80 heterodimer portion of the DNA-PK binds with high affinity to the end of double stranded DNA, and to a single stranded DNA transition (see 2nd full paragraph on p. 129), and recruits and activates the DNA catalytic subunit of the DNA-PK (see 3rd full paragraph on p. 129). Takiguchi teaches the role of Ku70 in DNA double strand repair (see bridging paragraph, pp. 133-134). Takiguchi teaches the motivation to establish experimental mouse models for studying the role of DNA-PK in human diseases (see last paragraph of the article, bridging pp. 133-134). Takiguchi therefore teaches a

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motivation to inhibit either mouse DNA-PK or human Ku70 in DNA-PK activity to study its role in human diseases, including the ability of a cell with DNA damage to repair strand breaks. This motivation, combined with the routine approach taught by Milner to design and test antisense in their ability to target and inhibit the expression of a target gene of known sequence (e.g. human Ku70) in vitro, renders the invention obvious.

Applicant argues that none of the cited references teaches the introduction of any antisense oligonucleotide into any cell for the purpose of increasing the susceptibility of the cell to DNA damaging agents. Applicant is correct that none of the references alone anticipates the claimed invention. The combined teachings, however, render the instant invention obvious. Takiguchi provides the motivation to target and inhibit the expression of Ku70 in humans (or in a mouse model) to study its role in various human diseases, and to study the role of Ku70 in DNA-PK's ability to repair strand breaks. It was well known in the art that when damaging agents are used to treat cells, strand breaks occur. Milner taught the routine approach to design and test antisense inhibition in a cell in vitro and Reeves teaches the nucleotide sequence of the target gene. It therefore would have been obvious to one of ordinary skill in the art to design antisense to inhibit the expression of the well known target gene Ku70 in vitro to study its role in repairing DNA strand breaks. It would have been obvious to compare the effect of DNA damaging agents on cells that have Ku70 expression with cells that lack Ku70 expression following the inhibition by antisense. For these reasons, the combined teachings of Takiguchi, Reeves, Milner and Au-Young render the instant invention obvious.

Claim Rejections - 35 USC § 112

Claims 1, 15, 16, 18-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 2-3-06.

Applicant argues that adequate description has been provided for the claimed invention, drawn to compositions and methods comprising an antisense oligonucleotide that specifically hybridizes with and inhibits the expression of human Ku70 because pertinent structural information has been provided in the specification. Applicant also argues that, although the sequence information may vary among species, members of the genus do not vary in the requisite structural features set forth in the claims. Contrary to Applicant's assertions, the scope of the claims includes numerous structural and the genus is highly variant because a significant number of structural differences between members of the given genus is permitted. Concise structural features (antisense or ribozyme sequences) that distinguish structures within the genus from those without, and a representative number of species that provide for the function claimed, of increasing the susceptibility of a target cell to DNA damaging agents upon administration of the compounds claimed, are missing from the disclosure and the claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed, drawn to antisense or ribozymes that specifically target and inhibit the expression of Ku70 in a cell, and provide for the cellular phenotype claimed. No antisense or ribozymes have been provided in the instant disclosure, including a representative number of species

encompassed by the broad genus claimed, that, upon administration to target cells, provide for the cellular phenotype claimed, of increasing the susceptibility of the cell to DNA damaging agents. Thus, Applicant was not in possession of the claimed genus.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. '1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara 6-20-06 JANE ZARA, PH.D.
PRIMARY EXAMINER